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Thrombotic Thrombocytopenic Purpura

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *This Medical Staff Conference will be devoted to a topic in hematology. We will begin with a case presentation by Ray Kacich, a medical student at the University of California.*

Case Presentation

MR. KACICH:† The patient, a 55-year-old Chinese woman, was transferred to the University of California, San Francisco (UCSF), Medical Center with a one-week history of petechiae, ecchymoses, intermittent fever and recurrent mental status changes. Two years before admission the patient had noted the onset of easy bruising, and an antifibrinolytic agent to be taken orally was prescribed.

Eleven days before transfer to UCSF, the patient arrived in San Francisco from Hong Kong with symptoms of headache, nausea, fatigue and dizziness. Over the next few days increased bruising developed and she was admitted to a local hospital where her physical examination findings were noteworthy for purpura. Laboratory studies elicited the following values: hematocrit 25 percent (normal, 37 to 48), reticulocyte count 7 percent (normal, 0.5 to 1.5) and platelet count 7,000 per cu mm (normal, 150,000 to 350,000). Coombs' tests, direct and indirect, were negative. The specimen from a bone marrow biopsy showed erythroid hyperplasia. A diagnosis of immune thrombocytopenic purpura with hemolytic anemia was entertained. The patient was discharged on a regimen of prednisone, 80 mg to be taken orally daily.

The morning after discharge, the patient was found in bed curled in a fetal position and talking unintelligibly. She was readmitted to the hospital with a temperature of 37.9°C. Physical examination showed new petechiae but there were no abnormalities on neurologic examination. A computerized tomography (CT) scan of the brain raised a slight suspicion of a left internal capsule lucency. Sensorium cleared spontaneously that evening. The next morning mental status again showed decline, and mild right facial weakness, right upper extremity drift and receptive aphasia were noted. The patient was transferred to UCSF.

On admission to UCSF, she was noted to be lethargic. Her blood pressure was 117/62 mm of mercury, pulse 96 a minute and regular, respirations 18 per minute and temperature 38°C. The

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ABBREVIATIONS USED IN TEXT

CT = computerized tomography
DIC = disseminated intravascular coagulation
HLA = human leukocyte antigen
LDH = lactate dehydrogenase
PAF = platelet-aggregating factor
PAFI = platelet-aggregating factor inhibitor
TTP = thrombotic thrombocytopenic purpura

patient had numerous petechiae and ecchymoses. Examination of head, eyes, ears, nose and throat was normal. The lungs were clear and the cardiovascular system appeared normal. Abdominal tone was increased with left upper quadrant tenderness. There was no organomegaly and bowel sounds were normal. Guaiac test of a stool was negative for occult blood. Neurologically the patient was symmetrically hyperreflexic, with probably decreased strength of the right extremities and an upgoing toe on the left.

Admission laboratory data included a leukocyte count of 12,600 per cu mm, hematocrit 24 percent, reticulocyte count 17 percent and platelet count 13,000 per cu mm. Results of coagulation studies were normal. Coombs' tests, direct and indirect, were negative. A peripheral blood smear showed numerous red cell fragments, nucleated red cells, spherocytes, myelocytes and increased numbers of reticulocytes. Analysis of urine specimen showed 2+ hemoglobin, with 10 to 25 red cells and white cells per high-power field. Chest x-ray films and electrocardiograms were normal. A diagnosis of thrombotic thrombocytopenic purpura (TTP) was made.

On her second hospital day the patient underwent placement of a Scribner shunt concurrent with a 10-unit platelet transfusion, followed by her first of seven plasmaphereses. Aspirin and dipyridamole therapy were begun and steroid doses were tapered. Within 12 hours of the first plasmapheresis the patient's condition was dramatically improved. By the fifth hospital day, after four plasmaphereses, she was asymptomatic and assessed by her family to be totally recovered. The platelet count had risen to 105,000 per cu mm and the peripheral blood smear showed fewer red cell fragments. On the sixth hospital day the patient began to relapse; lethargy and aphasia returned. The platelet count fell to 13,000 per cu mm and platelet transfusions did not raise this count. Plasmapheresis was restarted after a one-day lapse. Aspirin and dipyridamole therapy and heparin infusion into the Scribner shunt were discontinued. The patient also received intravenously methylprednisolone sodium succinate (Solu-Medrol), 1 gram, and vincristine sulfate, 2 mg. Mental status improved after plasmapheresis and the hematocrit, which had fallen 12 percent in the preceding 36 hours, became stable at 23 percent.

The next morning, hospital day 10, the patient had a generalized tonic-clonic seizure. Noncontrast CT scan of the head was normal, and she underwent her seventh plasmapheresis. After the procedure, the patient became hypotensive and was transferred to the Coronary Care Unit. Coagulation values became abnormal for the first time, platelet count fell to 1,000 per cu mm and the serum lactate dehydrogenase (LDH) level rose to 3,800 units per dl. The patient became anuric and hypotensive and died on that day.

Examination at autopsy showed a diffuse bleeding diathesis. Petechiae were noted in the endocardium, myocardium, pleura, esophagus, stomach, small bowel and liver. The lungs were moderately congested, and hemorrhage was present in the mediastinum, retroperitoneum and renal calices and pelvis. There were no gross lesions of the uncut brain. Brain cutting showed numerous petechiae in both hemispheres.

Microscopically, the characteristic lesions of TTP, finely granular hyaline thrombi of arterials showing a positive periodic acid-Schiff (PAS) reaction and associated with endothelial proliferation, were found in the heart, pancreas, adrenals, kidneys, alimentary tract, skin and brain.

DR. NAUGHTON: *This case and the subject in general of thrombotic thrombocytopenic purpura will now be discussed by Dr. Charles Linker.*

Discussion

DR. LINKER:* During the past five years, there has been greatly renewed interest in thrombotic thrombocytopenic purpura. The interest was initially prompted because of advances in therapy that were arrived at empirically. TTP now joins that small list of disorders that were once relentlessly fatal but can now be successfully treated in most instances. TTP has come under careful scrutiny in the laboratory, particularly because of the suggestion that a currently unknown plasma factor might be responsible for this bizarre disorder. At this time, the laboratory findings are

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tantalizing and interesting, but not definitive. The case presented here is an excellent example of the current state of our knowledge of TTP. Our therapy was almost successful but then failed. The crux of the problem is that it is difficult to treat a disorder when one does not understand its nature. I would like to review briefly the clinical characteristics of TTP and then discuss in detail two other aspects—the current state of therapy for the disorder and of investigation of its pathogenesis.

At present, TTP really cannot be precisely defined, and a definition has to be more or less descriptive. Thrombotic thrombocytopenic purpura is a syndrome characterized by a constellation of the classic pentad of findings: microangiopathic hemolytic anemia, thrombocytopenia, a variety of neurologic signs that often fluctuate, fever and some sort of renal disease.[1] TTP usually affects young people, with a slight female predominance (Table 1). Occasionally there is a prodromal flulike illness. A patient presents to a physician because of neurologic symptoms, bleeding, symptoms of anemia or abdominal complaints. At times the abdominal symptoms overshadow the others and a patient will undergo an exploratory laparotomy or be treated for inflammatory bowel disease before the hematologic aspects of the case are appreciated. Common findings on physical examination include fever, bleeding, pallor and a variety of neurologic findings.

Because the neurologic findings in this disease are so peculiar and so characteristic, they deserve a detailed description. There are often generalized findings of headache and decrease in level of consciousness, which may be as severe as coma. There are also focal symptoms of paresis, aphasias, dysarthrias and, usually in the terminal and uncontrolled phase of the disease, seizures. The most prominent aspect of the neurologic picture is that these findings can be evanescent. One may find a patient with a right hemiparesis, proceed to demonstrate this finding to a colleague, only to find the patient to be normal or to have a left hemiparesis. Similarly, one may find a patient with a classic receptive aphasia, leave the room and return to find the patient either in a normal state or comatose. Any theory of the pathogenesis of TTP must account for this unusual picture in which severe mental status and neurologic findings can come and go literally in a matter of minutes.

The diagnosis of TTP is made primarily by laboratory findings (Table 2). The hallmark of the disorder is microangiopathic hemolytic anemia characterized by an anemia that is usually severe, a reticulocytosis and, most importantly, red cell fragmentation on a peripheral blood smear. One will see burr cells and schistocytes, triangular forms and other varieties of abnormally shaped red blood cells that are thought to be produced by mechanical fragmentation. The diagnosis of TTP is untenable if red cell fragmentation is not an impressive part of the picture. Other concomitants of a hemolytic state may be present, including a high serum LDH, elevated bilirubin, hemoglobinuria and occasionally hemoglobinemia. Of importance is that the Coombs' test should be negative. Other laboratory features include thrombocytopenia that is usually severe and accounts for the bleeding disorder. The coagulation studies, by which I mean the prothrombin time, partial thromboplastin time, fibrinogen and thrombin time, should be normal. The presence of moderate amounts of fibrin-split products is a nonspecific finding and does not detract from the diagnosis of TTP.

Kinetic studies in TTP have shown that this is

TABLE 1.—*Clinical Features of Thrombotic Thrombocytopenic Purpura (TTP)*

Age: Usually 10-40 years
Sex: Female predominance (60%)
Occasional prodromal illness
Presenting symptoms
Neurologic symptoms
Bleeding
Pallor, weakness
Abdominal pain, nausea, vomiting
Findings on physical examination
Fever
Hemorrhage
Pallor
Neurologic findings

TABLE 2.—*Laboratory Features of Thrombotic Thrombocytopenic Purpura (TTP)*

Microangiopathic hemolytic anemia (MHA)
Anemia, often severe
Reticulocytosis
Red cell fragmentation
High lactate dehydrogenase
Negative Coombs' test
Elevated serum bilirubin level
Hemoglobinuria
Thrombocytopenia
Usually severe
Normal coagulation parameters
Except for elevated fibrin-split products
Abnormal urinary sediment

a disorder of accelerated platelet turnover, with normal fibrinogen turnover.[2] Platelet life is short and the calculated turnover is three to four times normal. Studies using radiolabeled platelets have shown that their uptake is not spread diffusely through the vascular system as one might expect, but rather it appears that injured platelets are taken up in the reticuloendothelial system. Red blood cell survival is short, as shown by studies of chromium-labeled red blood cells and by the clinical observation that red blood cell transfusion fails to raise the hematocrit level.

Our current concept of microangiopathic hemolytic anemia is illustrated by the rather striking picture of red cells that have been forced in vitro through a tube in which fibrin strands were created. These red cells are sheared across fibrin strands and then resealed in a variety of bizarre forms.

The histopathology of TTP is characterized by the *hyaline thrombus*. These thrombi are found throughout the vascular system, with predominant involvement of the brain, heart, kidney, pancreas and adrenal gland. These thrombi do not consist of red blood cells but of platelets and fibrin. This has been documented by electron microscopy and immunochemical staining. When the lesions are studied in detail by electron microscopy, one finds a spectrum of abnormalities: simple endothelial cell swelling, vessels with open lumens but subendothelial deposits of hyaline material, vessels with lumens occluded by loose platelet aggregates and, finally, occlusive thrombi. As one would expect from the description of the transient nature of the neurologic findings, infarction is seldom found.

In Amorosi and Ultmann's classic review in 1966,[1] most of the patients died within three months, and in their study of over 200 patients there were only 15 long-term survivors, defined as those surviving more than a year. Thus we have a composite clinical picture of TTP as a bizarre disorder affecting primarily young women, characterized by increased red cell and platelet turnover without participation of the coagulation system, in which available evidence appears to indict some abnormality of the platelet and the endothelial cell.

Before making a definitive diagnosis of a poorly characterized disease such as TTP, one must ask, "What else could it be?" Fortunately, most cases of TTP are fairly distinctive and the diagnosis is straightforward. Nevertheless, there are other disorders that can mimic some of its manifestations

TABLE 3.—*Differential Diagnoses of Thrombotic Thrombocytopenic Purpura (TTP)*

Disseminated intravascular coagulation (DIC)
Evans' syndrome
Vasculitis
Systemic lupus erythematosus
Severe glomerulonephritis
Other
Other causes of microangiopathic hemolytic anemia (MHA)
Vascular malformations
Prosthetic valves
Metastatic adenocarcinoma
Malignant hypertension
TTP-like syndromes
Hemolytic-uremic syndrome
Postpartum acute renal failure
Eclampsia

(Table 3). The most important disorder to exclude is disseminated intravascular coagulation (DIC), which certainly can lead to the presentation of an ill and febrile patient with bleeding and some red cell fragmentation. The important point to recognize is that DIC is primarily a disease of the coagulation system and that the coagulation tests should be grossly abnormal. With TTP, despite the severity of the illness and despite severe thrombocytopenia, there is no coagulopathy. Evans' syndrome describes the coexistence of immune thrombocytopenia and immune hemolytic anemia and could be confused with TTP. Importantly in TTP the Coombs' test should be negative, and in an immune-mediated process red cell fragmentation should not be present.

The vasculitic disorders can be the most difficult to differentiate from TTP. They share in common disruption of the endothelium—which may lead to platelet aggregation—and red cell fragmentation. Whatever the underlying cause of the endothelial abnormality, the resulting phenomena may appear similar. The distinction between TTP and vasculitis is best made on the basis of the composite clinical picture. On occasion a biopsy of involved vessels may be useful in making the diagnosis, inasmuch as the inflammatory lesion of vasculitis will appear quite different from the hyaline thrombus of TTP. In some cases the distinction between vasculitis and TTP becomes a matter of semantics; systemic lupus erythematosus occasionally causes a syndrome indistinguishable from TTP.

Because the microangiopathic finding is the laboratory hallmark of TTP, other causes of microangiopathy need to be considered. Vascular mal-

TABLE 4.—*Proposed Therapies for Thrombotic Thrombocytopenic Purpura (TTP)*

Steroid agents	Plasma infusion
Splenectomy	Vincristine sulfate
Antiplatelet agents	Prostacyclin infusion
Plasma exchange	

formations, prosthetic valves, metastatic adenocarcinoma and malignant hypertension are usually easy to distinguish from TTP, however. Lastly, what I have called the TTP-like syndromes may be difficult to separate definitively from TTP because one is dealing with a spectrum of disorders that most likely have the same underlying pathophysiology, rather than being totally different diseases. The adult form of hemolytic-uremic syndrome and its variant, postpartum acute renal failure, are part of a TTP-like spectrum. Eclampsia is usually distinctive but on occasion merges with TTP.

Treatment of TTP

Having made a definitive diagnosis, one must face the very difficult issue of treatment. The variety of proposed therapies is testimony to the fact that none is perfect (Table 4).

Glucocorticoid preparations alone are ineffective in this disorder. Because adrenal hemorrhage is commonly seen in thrombotic thrombocytopenic purpura, one can argue that a very ill patient should be given steroids to prevent addisonian crisis, but this is a secondary use of such treatment. Almost all patients with TTP receive steroids in addition to other therapies, so it is impossible to assess whether they may have some use in an adjunctive role. However, glucocorticoid agents should not be relied on as primary therapy.

Splenectomy is the time-honored form of treatment of TTP, and in Amorosi and Ultmann's review[1] the only patients with long-term survival were those treated with splenectomy. Dr. Cuttner[3] at Mt. Sinai Hospital has recently summarized her ten-year experience with splenectomy for TTP. Of 18 patients, 13 showed response, and when she excluded those patients who had not also received dextran intravenously, a very impressive 87 percent response rate was seen. Other investigators have also observed that patients respond to splenectomy, including those who have failed on a trial of plasma exchange. Despite these excellent results, most investigators do not recommend splenectomy as the first line of therapy for thrombotic thrombocytopenic purpura. Other groups have not seen a high response rate to splenectomy. Also, one must consider the problems of operating on an acutely ill patient with thrombocytopenia who may not benefit from platelet transfusions. Furthermore, less invasive procedures may be more or equally effective. I am convinced from published evidence that splenectomy does have some role in the treatment of TTP, but I reserve its use for patients who have failed to respond with primary therapy. The rationale for the use of splenectomy is obscure and its use is entirely empiric.

Antiplatelet agents have been used for over ten years in the treatment of TTP.[4] The rationale is clear. Patients with prosthetic valves have accelerated platelet turnover without accelerated fibinogen turnover, the same as in TTP. The combination of aspirin and dipyridamole can reduce systemic emboli and can correct the altered platelet turnover. Hence these drugs might be expected to correct the platelet disorders of TTP. Antiplatelet agents have been used occasionally as the sole form of therapy for TTP and some patients have responded. However, the bulk of information about antiplatelet agents concerns their use as the second, third, fourth or even fifth line of therapy in combination with other modalities. Several studies show[5] a beneficial effect of such therapy. Some patients treated with dipyridamole have not responded initially but eventually have to higher doses of this agent. Additionally, patients have appeared to respond to combinations of treatments, including antiplatelet agents, to relapse when the antiplatelet agents were withdrawn and to re-respond when they were reinstituted. Although antiplatelet agents have contributed to the treatment of some patients, their importance is difficult to assess. Certainly they should not be used as the only therapy. Whether their therapeutic benefit in some patients will outweigh the increased bleeding risk resulting from the addition of a platelet-inhibiting agent to a patient who is bleeding and has thrombocytopenia is currently unknown and can be answered only by careful clinical trials.

Considerable progress was made in the treatment of TTP in 1976 when Bukowski and coworkers[6] reported their results with exchange transfusion. Previous results with other forms of therapy, including steroids and splenectomy, were extremely disappointing, with a mortality in the range of 90 percent to 95 percent. With this new therapy, not only did some patients recover, but, almost like Lazarus, four of six patients recovered from coma or dense neurologic abnormalities

TABLE 5.—*Hypotheses Regarding Pathogenesis of Thrombotic Thrombocytopenic Purpura (TTP)*

Cytotoxic anti-endothelial cell antibodies
Absence of inhibitor of platelet aggregation
Absence of prostacyclin-stimulating factor
Absence of prostacyclin-stabilizing factor
Decreased fibrinolytic activity in endothelial cells

within 12 to 24 hours of exchange transfusion. The following year Bukowski and associates[7] reported the use of plasmapheresis without red cell transfusion but with similarly dramatic results. Other investigators[8] have also reported not only that a sizable fraction of patients (approximately 60 percent to 70 percent) respond to such therapy, but that dramatic recovery from coma and from other neurologic abnormalities may occur during or shortly after plasma exchange. It has been argued that we are misinterpreting the responses to plasma exchange and that improvement with therapy for TTP is the result of better support modalities and the recognition of milder cases. That argument is not tenable. Improved support is important and these patients do need blood products; however, the repeated observation of dramatic recovery during or immediately after plasma exchange is impressive, certainly to those involved in the care of these patients. My review of the literature has yielded 70 cases treated with plasma exchange, with a 70 percent response rate. Thus it is a therapy that works well in most cases. In some cases, as in the case discussed here, it fails. Because of its effectiveness, rapidity of action and relative lack of toxicity, plasma exchange is now the first line of therapy for TTP.

In 1977 Byrnes and Khurana[9] created a small sensation by reporting the effectiveness of simple plasma infusion for TTP. They treated a case of TTP with plasma exchange using fresh frozen plasma as the replacement fluid. When they used albumin alone as replacement, the patients relapsed. When they simply infused fresh plasma without plasma removal, the patients responded. In one patient either fresh frozen or outdated plasma would correct the disorder. In 1980 Byrnes[10] updated these results and reported 14 of 19 patients responding to plasma infusion as their sole therapy. Other investigators have confirmed these results in occasional patients, particularly those with chronic TTP. Upshaw[11] reported a case of a congenital TTP-like syndrome that responded to small-volume plasma infusion. However, many patients have failed on plasma infusion and then responded either to plasma exchange or to other forms of therapy, such as splenectomy and steroid agents.[12] At present, plasma infusion should not be used as the sole form of therapy for patients with typical fulminant TTP. Some will respond, but those who require additional therapy may deteriorate irreversibly while this therapy is failing. Plasmapheresis is a more inclusive treatment and should be used initially.

Recently two new modes of therapy for TTP have been described. The *Vinca rosea* alkaloids, vincristine and vinblastine, have been used with apparent success in eight reported cases. Some of these patients had failed to respond to more conventional treatment, and in some vincristine sulfate was the sole agent. The mechanism of action of vincristine in this circumstance is obscure and the role of this agent in therapy remains to be determined. Prostacyclin infusion has been attempted in several cases in which conventional treatment failed. The rationale for its use is clear: it should prevent the platelet aggregation that presumably causes vascular occlusions. This therapy has failed in several cases but has been successful in one instance. Information regarding the use of prostacyclin in this disorder is clearly preliminary.

Pathophysiology

I should like to move now to a discussion of the pathophysiology of TTP. Most students of TTP feel that an interaction between platelets and endothelial cells is responsible for the disorder. Whether the platelet aggregation abnormality is primary with secondary endothelial damage, or whether endothelial damage comes first and platelets adhere secondarily, or whether there is some subtle interaction between these two cell types is not at all clear. A number of hypotheses have been advanced regarding the precise mechanism (Table 5). From the large number of hypotheses proposed, it is clear that no explanation is widely accepted. At present, the following should be viewed as preliminary and as pertaining perhaps only to small subsets of TTP.

Some cases of TTP appear to be genetic in origin. The evidence for this is twofold. TTP has been reported several times in siblings. In some cases the disease has been unprovoked, but in one remarkable circumstance, fatal TTP developed in two sisters during their pregnancies. In adult hemolytic-uremic syndrome, a similar pattern of

sibling predisposition has been reported. In addition to these cases, reports of relapsing TTP have also been documented, suggesting that a patient may be prone to have the disorder develop but it may require some inciting event. The nature of the possible genetic predisposition is unknown. One report has suggested a human leukocyte antigen (HLA) linkage.

Kwaan[13] has proposed that a defect in vascular fibrinolytic activity is responsible for the disorder. He finds that endothelial cells from blood vessels of TTP patients have reduced ability to lyse fibrin when they are plated in vitro on fibrin-coated dishes. In contrast, endothelium adjacent to areas of "unusual" thromboses has normal or enhanced fibrinolytic activity in this assay. It is difficult to assign a causative significance to this observed phenomenon. Current assays of fibrinolytic activity may not be physiologically relevant. Also, decreased fibrinolytic activity could be a secondary phenomenon, the result of endothelial cell damage of any cause.

A circulating toxin to endothelial cells has been postulated as the primary problem in TTP. Wall and co-workers[14] have reported eight cases in which they showed an IgG antibody that would support complement-mediated lysis of endothelial cells in the presence of rabbit complement. Other investigators have reported similar findings. Problems with all these reports are that anti-HLA antibodies would also be detected in this system and that these patients are multiply transfused and often previously pregnant. At this time, the weight of evidence is against TTP's being an immunologic-mediated disorder. TTP cases during pregnancy have been associated with thrombi only in the maternal circulation; if an IgG factor were responsible one would expect the fetus to be affected as well.

Normal plasma may contain a previously unsuspected inhibitor of platelet aggregation (platelet-aggregating factor inhibitor, PAFI), with the defect in TTP being the absence of this inhibitor.[15] Observations by Lian and Savaraj in support of this are as follows: When they add TTP plasma to normal platelets that have been washed free of plasma proteins, the platelets agglutinate. Normal plasma does not cause this agglutination. This effect of TTP plasma is not inhibited by standard antiplatelet agents or by prostacyclin. The effect is neutralized by dilution of TTP plasma with normal plasma, and this correction is dose-dependent and time-dependent. Two different PAFI's—one an immunoglobulin and one with high molecular weight that can neutralize the platelet-aggregating effect of TTP plasma—were reported to be purified. Although Lian and Savaraj's concept is interesting, few investigators have reproduced their finding of the platelet-aggregating factor (PAF) in TTP plasma, and the finding is restricted to a small number of cases. Most cases appear to lack PAF. One strength of Lian and Savaraj's proposal is that it would explain the efficacy of plasma infusion therapy in the restoration of PAFI. This hypothesis is currently preliminary, however, and requires further development.

With all the recent interest in prostaglandin metabolites mediating the interaction between platelets and endothelial cells, prostacyclin metabolism became a logical target of inquiry in TTP. Remuzzi and associates[16] in 1980 made the following observations. When normal plasma is added to endothelial cells in culture, they are stimulated to make prostacyclin. TTP plasma lacks this stimulatory ability. After one patient was successfully treated with plasma exchange, this stimulatory defect was corrected. Even more interesting, another patient in remission had persistence of this defect and two of the four children of this patient had the same in vitro deficiency. Such a deficiency might explain the apparently genetic predisposition to TTP. One other investigation has confirmed these results.[17] Prostacyclin is far more stable in plasma than it is in buffer for reasons that are unclear. Chen and co-workers[17] have reported that this enhanced prostacyclin stability is not mediated by TTP plasma but that the defect is corrected by the addition of normal plasma. Wu and colleagues[18] have studied radiolabeled prostacyclin that has been incubated with normal plasma and fractionated by gel filtration. In normal plasma, prostacyclin binds to a very high molecular weight component that elutes in the void volume. This high molecular weight factor was absent in TTP plasma. These studies regarding prostacyclin must be viewed cautiously. There may be no normal circulating endogenous prostacyclin. If this is true, observations concerning the fate of exogenous prostacyclin may not be physiologically relevant.

Conclusion

The TTP syndrome represents a heterogeneous spectrum of abnormalities, some of which are chronic and possibly hereditary, but most of which are fulminant. Although the pathogenesis appears

to operate through a final common pathway of platelet-endothelial cell interaction that causes vessel occlusion, several different basic mechanisms likely lead to the same result. The basis of this disorder remains obscure. The current therapy of choice for this disorder is frequent large-volume plasma exchange using fresh frozen plasma as the replacement fluid. We currently perform exchanges daily, each time replacing a volume equal to 1½ to 2 times a patient's calculated plasma volume. Plasmapheresis is continued until a patient achieves clinical and hematologic remission. Red cell fragmentation may continue to be apparent on a peripheral blood smear for prolonged periods and is not by itself an indication for continuing treatment. In our experience maintenance therapy is usually not necessary.

Whether adjunctive therapy with antiplatelet agents or other modalities help more than they hurt cannot yet be answered but will likely be addressed in ongoing clinical trials. The efficacy of other therapeutic agents such as vincristine is also uncertain. However, in approaching a patient with TTP, one must be open-minded with regard to changing treatment regimens that are not rapidly effective. Because TTP is a heterogeneous disorder, different patients respond to different therapies. If a patient is not responding well to first-line therapy, this must be quickly recognized and a different approach taken. The combination of splenectomy, dextran and glucocorticoid agents is the second-line therapy of choice. Definitive therapy for TTP awaits the elucidation of the basic pathophysiology of the disease.

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